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**THE RELATIONSHIP BETWEEN THE DIETARY INFLAMMATORY INDEX
AND INCIDENT FRAILTY: A LONGITUDINAL COHORT STUDY**

ABSTRACT

Objective: Inflammation is key risk factor for several conditions in the elderly. However, the relationship between inflammation and frailty is still unclear. We investigated whether higher dietary inflammatory index (DII) scores were associated with higher incidence of frailty in a cohort of North Americans.

Design: Longitudinal with a follow-up of 8 years.

Setting: Osteoarthritis Initiative.

Participants: 4,421 participants with knee osteoarthritis or at high risk.

Measurements: DII scores were calculated using the validated Block Brief 2000 Food-Frequency Questionnaire and categorized into sex-specific quartiles. Frailty was defined as two out of three of the criteria of the Study of Osteoporotic Fracture study (i.e. weight loss, inability to rise from a chair five times, and poor energy). The strength of the association between baseline DII score and incident frailty was assessed through a Cox's regression analysis, adjusted for potential baseline confounders, and reported as hazard ratios (HRs).

Results: A total of 4,421 community-dwelling participants (2,564 females; mean age: 61.3 years) without frailty at baseline were identified from the Osteoarthritis Initiative. During 8 years of follow-up, 356 individuals developed frailty (=8.2%). Using Cox's regression analysis, adjusting for 11 potential confounders, participants with the highest DII score (Quartile 4) had a significantly higher risk of experiencing frailty (HR: HR: 1.37; 95% CI: 1.01-1.89; p=0.04) compared to participants with the lowest DII score (Quartile 1). The association between DII score and frailty was significant only in men.

Conclusion: Higher DII scores, indicating a more pro-inflammatory diet, are associated with higher incidence of frailty, particularly in men.

Keywords: aged; dietary inflammatory index; frailty; inflammation.

INTRODUCTION

Frailty is typically defined as an age-associated decline in reserve and function that result in a reduced ability to cope with acute or external stressors faced every day.¹ Frailty is a common condition in the elderly, with a prevalence of 10% for those older than 65 years and 30% for those older than 80 years.^{2,3} Frailty is significantly associated with several deleterious outcomes in the elderly, including depression^{4,5}, cardiovascular disease⁶, hospitalization⁷ and, in some instances, mortality.⁸ Consequently, understanding, preventing and managing frailty in older adults is of high importance.

Despite this increasing interest in frailty, the pathophysiological changes underlying and preceding frailty are still largely unknown. Serum markers of inflammation linearly increase with age⁹ probably due to a combination of factors, such as decline in immune function¹⁰ and increase in medical conditions (e.g. osteoarthritis, dementia, cardiovascular disease) associated with inflammation¹¹. Inflammation is also associated with low muscular performance¹² and it has been proposed that this condition may be closely linked with frailty.¹³ From a molecular point of view, pro-inflammatory cytokines may influence frailty either directly by promoting protein degradation, or indirectly, by affecting important metabolic pathways.¹⁴ However, the evidence regarding inflammation and frailty in human beings is still conflicting. In a recent systematic review and meta-analysis, we found that in 32 cross-sectional studies both frail and pre-frail participants had significantly higher levels of inflammatory markers.¹⁵ However, in four longitudinal studies¹⁶⁻¹⁹, higher inflammatory markers were not associated with any increased risk of frailty at follow-up, suggesting that additional findings from longitudinal studies are needed.

Diet is a key source of inflammation and the Dietary Inflammatory Index (DII) is a literature-derived dietary tool, useful for assessing the overall inflammatory potential of individual's diet.²⁰ Higher DII values are strongly correlated with serum inflammatory markers, suggesting a close

relationship between this index and bio-humoral inflammatory parameters.²¹ The DII has also been used to assess the relationship between diet quality related to inflammation and several chronic inflammation-related outcomes, such as metabolic and respiratory diseases, cancer and fractures.²²⁻²⁵ However, no study has yet explored the association between DII and frailty. Therefore, the purpose of this study was to investigate whether increasing DII scores are associated with increased incidence of frailty, using a large cohort of North American adults.

MATERIALS AND METHODS

Data source and subjects

Data were included from the Osteoarthritis Initiative (OAI) database. The OAI is freely available (<http://www.oai.ucsf.edu/>). Within the OAI, potential participants were recruited across four clinical sites in the United States of America (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. In this database, we identified people who either: (1) had knee OA with knee pain for a 30-day period in the past 12 months or (2) were at high risk of developing knee OA²⁶ with data collected during baseline and screening evaluations in November 2008. All participants provided informed written consent.

The OAI study was given full ethical approval by the institutional review board of the OAI Coordinating Center, at University of California in San Francisco.

Dietary data and Dietary inflammatory index (exposure)

Dietary intake was assessed using a validated tool, the Block Brief 2000 Food Frequency Questionnaire (FFQ) during the baseline visit.²⁷ Seventy items were assessed to determine an individual's typical food and beverage consumption over the past year. The frequency of consumption was reported at nine levels of intake from "never" to "every day". In addition, seven dietary behavior questions were asked regarding food preparation methods and fat intake, one question on fiber intake, and 13 questions on vitamin and mineral intakes.

The details of development of DII is described by Shivappa *et al.* elsewhere.²⁰ High sensitivity CRP measurements were used to examine construct validity of the DII in a longitudinal cohort using multiple (up to 15) 24-hour dietary recall interviews and up to five 7-day dietary recalls. The DII was subsequently validated in four studies among different populations with a variety of inflammatory biomarkers (i.e., interleukin, IL-6, hs-CRP, fibrinogen, homocysteine and TNF- α).^{21,28-32} In this updated version of the DII, 1943 articles were reviewed and scored. Forty-five food

parameters, including foods, nutrients, and other bioactive compounds, were identified based on their inflammatory effect on six specific inflammatory markers, including CRP, IL-1 β , IL-4, IL-6, IL-10 and tumor necrosis factor (TNF)- α . A regionally representative world database representing diet surveys from 11 countries was used as a comparative standard for each of the 45 parameters (i.e. foods, nutrients, and other food components). Intake values from this database were used to calculate the DII scores. This is explained in more detail in the DII Methods paper.²⁰ Briefly, a standard mean for each parameter from the representative world database was subtracted from the actual individual exposure and divided by its standard deviation to generate Z scores. These Z scores were converted to proportions (thus minimizing effects of outliers/right- skewing). These values were then doubled and 1 was subtracted to achieve symmetrical distribution with values centered on 0. The resulting value was then multiplied by the corresponding inflammatory score for each food parameter and summed across all food parameters, to obtain the overall DII score. Using the FFQ, we calculated the DII based on energy-adjusted intake of the 24 single food parameters of the 45 possible food parameters that were available from the FFQ using the energy density approach, which calculated the DII per 4184 kJ (1000 kcal) of energy.³³ The 24 food parameters available for DII calculation in this study were vitamin B₁₂, vitamin B₆, β -carotene, carbohydrate, cholesterol, fat, fibre, folic acid, iron, magnesium, monounsaturated fat acids (MUFA), niacin, protein, polyunsaturated fatty acids (PUFA), riboflavin, saturated fat acids(SFA), selenium, thiamin, vitamin A, vitamin C, vitamin E, vitamin D, zinc, niacin, and caffeine.

Outcome

The study's outcome of interest was incident frailty. In accordance with the Study of Osteoporotic Fracture (SOF) index^{34,35} frailty was defined as the presence of ≥ 2 out of three of the following criteria: (i) weight loss $\geq 5\%$ taking place between baseline and the follow-up examinations (at the baseline examination a body mass index, BMI, of less than 20 Kg/m², a common cut-off for identifying underweight people the elderly³⁶, was used, since no information regarding weight

changes were recorded); (ii) the inability to rise from a chair five times without arm support (hereafter referred to as inability to carry out chair stands); and (iii) poor energy based on the SF12 questionnaire response of “little at a time” or “none at a time” to the question “in the past 4 weeks, did you have a lot of energy?” The assessment of the outcome was made at the baseline and during the V01 (12 months), V03 (24 months), V05 (36 months), V06 (48 months), V08 (72 months) and V10 (96 months).

Covariates

Ten covariates (other than the number of frailty indexes at baseline) were identified *a priori* as potential confounding factors. These included: body mass index (BMI); physical activity evaluated using the total score for the Physical Activity Scale for the Elderly scale (PASE)³⁷; race; smoking habit; educational attainment level (college or higher vs. others); yearly income (< or ≥ \$50,000 or missing data); depressive symptoms assessed with the Center for Epidemiologic Studies Depression Scale (CES-D)³⁸; and a validated general health measure of self-reported comorbidities assessed through the modified Charlson Comorbidity Index score.³⁹

Statistical analyses

Data on continuous variables were normally distributed according to the Kolmogorov-Smirnov test. Data were presented as means and standard deviation values (SD) for quantitative measures, and frequency and percentages for all discrete variables. For descriptive purposes, only the data regarding the lowest and the highest quartiles are reported. Since the interaction sex by DII scores was significant ($p < 0.05$) in predicting frailty at follow-up, the data are presented also by gender. Levene's test was used to test the homoscedasticity of variances and, if its assumption was violated, Welch's ANOVA was used. P-values were calculated using the Jonckheere-Terpstra test⁴⁰ for continuous variables and the Mantel-Haenszel Chi-square test for categorical variables.

To assess the relationship between DII score and incident frailty, a Cox's regression analysis was conducted where the incident frailty was defined as the discrete 'outcome,' time-to-event was the temporal factor, and the DII score was the 'exposure'. Deceased people were censored. DII also was categorized into gender-specific quartiles, with Quartile 1 (=lowest DII) representing the reference group. The basic model was not adjusted for any confounders. The fully adjusted model included the following covariates: age (as continuous); sex (only for the analyses for the sample as whole); race (Whites vs. others); BMI (as continuous); education (\geq college degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as \geq or $<$ US\$50,000 or missing data); Charlson Comorbidity Index; PASE score (as continuous); CES-D (as continuous); number of frailty indexes at baseline (one vs. none).

Multi-collinearity among covariates was assessed through variance inflation factor (VIF) ⁴¹, taking a cut-off of 2 as the criterion for exclusion. No covariates met this criterion and therefore none was excluded for this reason. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated to estimate the strength of the associations between DII score (reported as quartiles) and incident frailty. P values for trend were calculated across DII groups using the Wald test, based on a score derived from the median value of each baseline DII group. We finally modelled DII as continuous variable, reporting the association between increase in one SD as exposure variable.

Several sensitivity analyses were conducted evaluating the interaction between DII score and selected factors [i.e., age below or more/equal than 65 years, overweight/obese ($\geq 25\text{kg/m}^2$) vs. normal weight ($18.5\text{kg/m}^2 < \text{BMI} \leq 25\text{kg/m}^2$), yearly income, gender, race, education, smoking habits, yearly income, number of frailty index at baseline categorized as one vs. none) in the association with frailty, but only sex emerged as moderator of our findings ($p < 0.05$ for the interaction).

A $p < 0.05$ was deemed statistically significant. All analyses were performed using SPSS[®] software version 21.0 for Windows (SPSS Inc., Chicago, Illinois).

RESULTS

Sample selection

The OAI dataset initially included a total of 4,796 individuals. For 129 participants, there was insufficient data to calculate DII or an unreliable caloric intake was recorded (<500 or >5000 Kcal/day) (n=62). Finally, data from another 184 participants were lost during follow-up (they did not have sufficient information regarding frailty items). Accordingly, 4,421 participants were included in analyses.

Descriptive characteristics

The cohort consisted of 2,564 females (58.0%). Mean age was 61.3 years (± 9.3 years; range: 45-79 years) and mean DII was -3.17 (± 1.67 points; range: -5.65 to 3.70).

Table 1 illustrates the baseline characteristics by DII quartiles in the sample as whole and by gender. Those in the highest DII quartile (reflecting the most pro-inflammatory diets) were significantly younger and have lower educational attainment than other participants. Participants with higher DII levels were more likely to be smokers (only in women), non-White, obese (as shown by higher BMI values), and depressed compared to individuals in other quartiles (**Table 1**). Individuals with higher DII values had a significantly higher prevalence of poor physical performance (p for trend<0.0001), but lower presence of weight loss (p for trend=0.002), even if this last finding was limited only in women (p for trend<0.0001). There no differences across DII groups with respect to poor chair stands time.

Dietary inflammatory index and incident frailty

Over a mean follow-up of 8 years, 356 individuals (118 men and 238 women; =8.2% of the baseline population) became frail; for a global incidence of 12 (95%CI: 10-14) people for 1,000 persons-years.

Cox's regression analysis, adjusting for 11 potential confounders at baseline, with the lowest DII as reference (=Q1), showed that participants with the highest DII score (=Q4) had a significantly higher probability of incident frailty (HR: 1.37; 95% CI: 1.01-1.89; $p=0.04$; **Table 2**). However, the p for trend did not reach the statistical significance (p for trend= 0.27). In the multivariate analysis, other factors significantly associated with the onset of frailty were: BMI (HR: 1.05; 95% CI: 1.03 to 1.07; $p<0.0001$), CES-D (HR: 1.06; 95% CI: 1.05 to 1.07; $p<0.0001$), Charlson co-morbidity index (HR: 1.20; 95% CI: 1.10 to 1.31; $p<0.0001$); presence of one frailty item at baseline (HR=2.76; 95%CI: 2.15 to 3.56; $p<0.0001$). Increase in one SD of DII (=1.67 points) did not increase the risk of frailty at follow-up (adjusted HR=1.04; 95%CI: 0.93-1.15; $p=0.51$).

Because the interaction of sex by DII in predicting frailty at follow-up was significant (p for interaction= 0.03), the results also are reported by gender in **Table 2**. In men, all the higher quartiles of DII were associated with incident frailty (HR=3.24; 95%CI. 1.38-7.57; $p=0.007$ for the second quartile; HR=3.21; 95%CI. 1.41-7.31; $p=0.006$ for the third quartile; HR=4.03; 95%CI. 1.78-9.09; $p<0.0001$ for the highest quartile; p for trend <0.0001). No association was, on the contrary, observed in women (p for trend= 0.24). These results are graphically reported for men in **Figure 1**. Each increase in one SD in DII score increased the risk of frailty in men (adjusted HR=1.24; 95%CI: 1.06-1.46; $p=0.008$), but not in women (HR=0.92; 95%CI: 0.80-1.05; $p=0.22$).

DISCUSSION

In this longitudinal study, we found that higher DII values were associated with greater incidence of frailty. During a follow-up period of 8 years, after adjusting for several potential confounders at baseline, individuals with the highest DII score (i.e. having a more pro-inflammatory diet) had a 37% higher risk of frailty. This association, however, was significant only in men, suggesting important gender differences.

The relationship between inflammation and frailty is complex, since both increase exponentially with advancing age and because both higher levels of inflammation and frailty are associated with several chronic disease outcomes in the elderly.⁴²⁻⁴⁴ These findings suggest that common pathways are present in frailty and inflammation. Compared to healthy participants, frail people seem to have a significant reduction in both innate and acquired immunity.⁴⁵ Additionally, an increase in mitochondrial activity is seen with an increase in oxidative stress products⁴⁶, ultimately leading to an increase in serum inflammatory levels.

Previous longitudinal studies did not globally show a significant association between higher levels of inflammatory and endocrine markers and the onset of frailty.¹⁶⁻¹⁹ The absence of an unified operational definition for frailty makes the development of measurable biomarkers of particular importance.⁴⁷ The ability of higher inflammatory parameters to predict the onset of frailty could be important because higher levels of these inflammatory markers significantly contribute to transitions from frailty to disability.⁸ We can hypothesize that previous longitudinal studies did not report any significant association because they used biohumoral estimates of inflammation that are very sensitive to acute and sub-acute diseases. Therefore, unlike DII scores, which may better reflect long-term habitual exposure, they may not be sufficiently stable for use in epidemiologic studies.

Another important finding of our study is that higher DII scores are associated with incident frailty in men, but not in women. In men, for example, participants in the highest quartile had four times higher risk of developing frailty during follow-up period. We also observed men to have higher DII scores compared to women. We can hypothesize that inflammation has a differential effect in predicting chronic disease outcomes between genders in agreement with the current literature. For example, the prognosis for females suffering from inflammatory conditions seems to be better than in males, even if inflammatory markers are usually higher in females than in males, particularly after menopause.^{48,49} It also has been shown in the past that women consume healthier diets rich in fruits and vegetables compared to men; so, there could be other factors which influence development of frailty in women.⁵⁰ However, future research is needed to explore the significant difference between genders in this study.

Our findings might have important clinical consequences. Inflammation is known to be a significant risk factor for several medical conditions typical of older people, a phenomenon recently called “inflammaging”.⁵¹ Since DII is linearly associated with serum markers of inflammation^{21,28-32}, the possibility of modulating inflammation with a healthier diet might provide important benefits for preventing frailty, particularly in men for which, as mentioned before, unhealthier diets are probably more common than in women.⁵⁰ Unfortunately, very few randomized controlled trials regarding the possible role of anti-inflammatory diets are available and, where available, these interventions are usually associated with a physical exercise regimen.^{52,53} Future studies with diets with a strong anti-inflammatory meaning (such as Mediterranean diet) are needed in this sense.

The findings of our research should be considered in the light of its limitations. The principal shortcoming is that we used a different definition of frailty between baseline and follow-up, because weight loss was defined in different ways. This could introduce an important bias in our results. Second, the comorbid medical conditions assessed in this study were self-reported, introducing a

possible recall bias. Another limitation could be the non-availability of data on the remaining 21 food parameters of the DII. Some components such as turmeric, saffron and eugenol are not consumed in high quantity in this population, so non-availability of these food parameters may not have played major role in this association. However, inclusion of parameters such as flavonoids, which are commonly consumed, may influence the results. Finally, the findings deriving from the OAI are not fully generalizable to other populations because this database includes only people having or at high risk of knee OA. Despite these limitations, this study is one of the few reporting data on the association between inflammation and frailty. It also is the first assessing the role of DII in this condition.

CONCLUSION

Higher dietary inflammatory index scores were associated with a higher incidence of frailty, even after considering several potentially important confounders measured at baseline. These findings were particularly strong in men suggesting important differences between genders. Future randomized controlled trials with diets rich in anti-inflammatory compounds are needed to confirm our findings.

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Conflict of interest: Dr. JRH owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. NS is an employee of CHI.

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FIGURE LEGEND

Figure 1. Association between dietary inflammatory index and incident frailty in men.

Figure legend: blue line indicates the first quartile (i.e., participants with lower DII); yellow line those in the second, green those in the third and violet line participants with the highest DII values.